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14. ABSTRACT

With support from TATRC and under the leadership of the Principal Investigator, Dr. Richard W. Linton, a multidisciplinary team of researchers from the University of Oregon propose development of innovative and novel means to improve neurorehabilitation for amputees and treatment for patients at remote sites with acute brain injury. Results from the studies proposed here will move discoveries in basic neuroscience related to brain plasticity into translational level information and technologies aimed at addressing issues in neurorehabilitation due to loss of limbs and ameliorating emergency medical conditions which often occur at sites remote from immediate high level medical care.

In this application we have two related aims: 1) neurorehabilitation and 2) neuroinformatics and telemedicine. In aim one, we propose applying existing fMRI methods to rehabilitation of injuries that directly (e.g., traumatic brain injury) or indirectly (e.g., spinal cord injury or limb amputation) affect the organization of brain functions. In addition, we propose the development of lines of transgenic mice that reversibly model the effects of damage to specific brain regions with anatomical control for surpassing surgical lesions. In aim two, we propose to use our research on brain plasticity as a vehicle for the development of improved flow of information from injury site to tertiary

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University of Oregon
Brain Biology Machine Initiative
Developing Innovative Novel Methods to Improve Neuro-Rehabilitation for Amputees and Treatment for Patients at Remote Sites with Acute Brain Injury

Annual Report, Year Three
(8/15/2009 - 8/14/2010)

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INTRODUCTION

The Brain Biology Machine Initiative (BBMI) at the University of Oregon has the overall goal of using its strengths in molecular biology, neuroscience, and neuroimaging to understand how genes and experience build the networks underlying complex human activity. With support from TATRC and under the leadership of the Principal Investigator, Dr. Richard W. Linton, a multidisciplinary team of researchers from the University of Oregon proposed the development of innovative and novel means to improve neurorehabilitation for amputees and treatment of patients at remote sites with acute brain. Results from these studies will move discoveries in basic neuroscience related to brain plasticity into translational level information and technologies aimed at addressing issues in neurorehabilitation due to loss of limbs and ameliorating emergency medical conditions which often occur at sites remote from immediate high level medical care. ***This report covers the period August 15, 2009 through August 14, 2010, and is reflective of the relevant quarterly reports submitted during that period.***

SUMMARY OF PROPOSAL AND ACHIEVEMENTS IN YEAR 3 (JULY 1, 2009 – JUNE 30, 2010)

As described in the 2006-2007 proposal, "BBMI: Developing innovative and novel methods to improve neurorehabilitation for amputees and treatment for patients at remote sites with acute brain injury," UO researchers articulated two related aims: 1) neurorehabilitation and 2) neuroinformatics and telemedicine.

In aim one, we applied existing fMRI methods to rehabilitation of injuries that directly (e.g., traumatic brain injury) or indirectly (e.g., spinal cord injury or limb amputation) affect the organization of brain functions. Our work during the funding period contributed information on how amputation affects brain functioning and structure, particularly "higher-order" processes in the premotor and parietal regions. We developed statistical tools to assist with the characterization of brain reorganization following amputation. We achieved a greater understanding of how traumatic brain injury (TBI) affects brain networks related to executive function. Finally, we developed lines of transgenic mice that reversibly model the effects of damage to specific brain regions with anatomical control for surpassing surgical lesions, a key achievement that facilitated our *in vitro* work.

In aim two, we used our research on brain plasticity as a vehicle to better represent the flow of information, from injury site to tertiary care centers. This work involved the development of a set of tools to process neuroinformatic data based on dense-array EEG and high-resolution neuroimaging, which was based on electromagnetic head modeling. To this end, we

successfully developed an initial version of the Matlab signal analysis toolkit object-oriented framework. We deployed the NEMO database for the first time and made headway on the development of a NEMO portal. Our efforts to visualize the NIC workflow enabled us to implement workflows for other TATRC projects, and provided a foundation for the development of a web-services front end that will enable the integration of new applications into the workflow system. In the area of MRI imaging analysis, we developed BrainK tool capabilities, completed work on the alignment of CG and MRI images, and completed MRI image scanning. We also developed a database to deploy full head model construction and conductivity processing.

AIM 1: NEUROREHABILITATION

Project 1: Effects of bimanual visual feedback on sensory motor organization in unilateral amputees.
Project 2: Understanding the consequences of traumatic brain injury on individual brain networks related to executive function.
Project 3: Developing mouse lines capable of reversibly expressing transgenes with an anatomical specificity relevant to neurorehabilitation strategies in humans.

AIM 2: TELEMEDICINE AND NEUROINFORMATICS

Project 1: High Performance Signal Analysis Toolkit (HiPerSat) for dense array EEG.
Project 2: MRI and CT registration for accurate source analysis.
Project 3: Head tissue conductivity analysis.

Below are the specific deliverables outlined in our proposal for the grant period.

AIM 1: NEUROREHABILITATION

Project 1 Deliverable: This project will lead to an inexpensive, portable and easily deployed intervention for the prevention and treatment of phantom limb pain.
Project 2 Deliverable: This project will provide new insight into the relationship between functional deficits following mild traumatic brain injury (mTBI) and the underlying changes in brain activation. This has the potential to enhance the development of mTBI assessment and may provide a useful set of tasks for improving executive functions in these patients.
Project 3 Deliverable: This project aims to produce mouse lines that will be powerful tools for the analysis of central neural circuits, which are necessary to promote enhancements to rehabilitative strategies in human patient populations.

AIM 2: TELEMEDICINE AND NEUROINFORMATICS

Project 1 Deliverable: the aim of this project is to have automated extraction of eyeblink, eye movement artifacts, head movement and electromagnetic interference from the

electroencephalography (EEG) recordings. Successful implementation and test at Electrical Geodesics, Inc. (EGI), Lewis Center for Neuroimaging (LCNI), and Harborview Hospital (Seattle, WA) will satisfy the criterion for HiPerSat deliverable.
Project 2 Deliverable: This project will provide the following: automated magnetic resonance (MR) and computed tomography CT image segmentation as a medical service; automated cortical surface extraction and dipole fitting to support electrical source analysis as a clinical service; and brain atlas registration as a research service to support the creation of both normative and pathological neuroinformatics databases.
Project 3 Deliverable: The aim of this project is to implement conductivity scanning as a routine medical service to allow accurate electrical source analysis of brain activity for neurosurgical planning.

In this, the **third** year of the grant period we are pleased to report that our projects are substantially on target to meeting the goals listed in the original proposal. Details are included in the Key Research Accomplishments and the Major Reportable Outcomes Sections, following.

KEY RESEARCH ACCOMPLISHMENTS

Aim 1: Neurorehabilitation

Project 1: Effects of bimanual visual feedback on sensory-motor organization in unilateral amputees (PI: Frey)

In the summer of 2009, we collected both behavioral and functional MRI data from 15 traumatic, upper-extremity amputees. In addition to the recruitment and scheduling, testing sessions lasted several hours per participant. We began to process the behavioral and fMRI data. We prepared a presentation of earlier work on upper extremity amputees for a Society for Neuroscience meeting.

We conducted an international search and successfully recruited a new postdoctoral fellow (Dr. Benjamin Philip) to work on this project.

In the fall of 2009 and winter of 2010, we analyzed functional MRI data from 15 traumatic, upper-extremity amputees and matched controls. Drs. Smith and Frey used advanced multi-variate statistical techniques (independent components analysis (ICA) both to detect and eliminate artifacts related to head motion and determine brain responses related to experimental manipulations. Examples of initial results for 7 right hand amputees were illustrated in the January 2010 report. For each simple movement task (performed in the absence of vision), we saw somatotopic increases (warm hues) associated with the moving

body segment in primary sensory and motor cortices. In all conditions except for elbow flexion of the residual limb, we also saw task-correlated deactivations (cool hues) in somatoptic representations of adjacent body parts.

Additional data collection and analyses were necessary to evaluate the relationship between these findings and cortical plasticity due to unilateral deafferentiation. Our initial assessment was that the cortical representation of the residual forelimb (assessed through right elbow flexion) expanded in the medial direction due to loss of afferent input and consequent changes in cortical inhibition.

Technical difficulties with the newly developed fMRI compatible somatosensory stimulator were resolved, and we invited amputees back to redo testing and recruited more amputees into the entire protocol.

In winter 2010, we scheduled and collected behavioral (sensory, cognitive) and MRI (structural and functional) data from additional unilateral, upper extremity amputees.

In the fall of 2009 and winter of 2010, Mr. Mattia Morangon worked with Dr. Frey to complete analyses of sensory data collected from 14 unilateral amputees. It was hypothesized that sensitivity changes should occur in relation to previously detected expansions of residual forelimb and face maps in the cortex following amputation. As noted in the quarterly reports, we failed to detect any such changes despite using a wide array of tests on each side of the face and intact hand, (static and moving 2-point discrimination, sensory threshold filament testing, stimulus localization testing, grating orientation task). Put differently, we find no evidence to suggest that expanded cortical representations of the face and/or residual forelimb translate into improved sensory functions.

In the fall of 2009 and winter of 2010, Dr. Benjamin Philip worked with Dr. Frey to design and pilot initial behavioral tasks that probe the effects of unilateral UE amputation on the ability to plan movements of the former hand and arm. This work was initially undertaken in healthy controls in preparation for use with our patients. Pending the outcome, an fMRI study will be undertaken.

In the fall of 2009 and winter of 2010, Ph.D. student Sergei Bogdanov and Dr. Frey worked together on two manuscripts related to previously collected structural and functional MRI data from amputees and matched controls. The first reports data from 11 unilateral amputees and matched controls during performance with the mirror box in fMRI. We found that imaging movements of the missing limb, paired with observation of reflected images of the moving intact hand, induced substantial activity with sensory and motor regions of the hemisphere contralateral to the amputation. The second reports analyses of the integrity of spino-cortical tracts. We found significant changes in diffusion tensor imaging (DTI) data from patients with

congenital limb absence but not in those who have lost a limb traumatically. This manuscript is presently under review at the journal *Brain.*

As noted in previous quarterly reports, we continued to grow our database of potential amputees for research and now have over 70 individuals with upper and/or lower extremity amputation(s), or congenital limb deficiencies, who have expressed interest in participating in this work. To save funds we are initially concentrating our efforts on local respondents.

in spring of 2010, we made significant progress on three main fronts: 1) Characterizing the behavioral effects of unilateral upper extremity amputation of movement planning processes (Philip & Frey); 2) Effects of unilateral upper extremity amputation on brain functional and macroscopic gray matter structure; and 3) Multivariate statistical approaches to characterization of sensory-motor reorganization following unilateral upper extremity limb amputation.

In the final months of the reporting period, the Frey lab reported the following progress:

1. Characterizing the behavioral effects of unilaterial upper extremity amputation of movement planning processes (Philip & Frey). It is well-known that limb amputation induces significant reorganizational changes in primary sensory and motor regions of the brain. However, there is virtually no data on how amputation affects higher-level movement planning processes that involve "higher-order" premotor and parietal regions of the brain. Yet, this knowledge is vital for developing efficient brain-controlled interfaces (BCIs) and training programs for the next generation of neurally-controlled prostheses. Toward this end, we conducted a series of behavioral studies targeting this question:

A. Grip Selection. In spring of 2010 we collected data from 9 amputees and 4 matched controls. Our data showed that amputees retain the ability to predict how best to grasp a handle (over- or under-hand) appearing in a variety of orientations despite years or decades without their amputated limb. In fact, we found differences in performance of this planning task between decisions based on use of the amputated vs. intact hand, or between amputees and matched controls (see Figure 1 in the quarterly report). This suggested that adaptation to prosthetics may be faster if the devices closely match the missing limb's joint (mechanical) constraints. This work was accepted for presentation at the Annual Meeting for the Society for Neuroscience in November, 2010.

B. Simon Effect. Our data on this project showed that amputees respond faster to visual stimuli when choosing a motor response on the same side. This matches the classical Simon effect, demonstrating that amputees' response selection processes remain intact despite their practice interacting with nearby space using only one hand. This suggested that limb amputation does

not reorganize the representations of the sensorimotor workspace, a fact that may be of considerable relevance in understanding adaptation to prosthetic limbs.

C. Inter-manual transfer of unimanual skills to the non-dominant hand following unilateral, dominant side amputation. Much attention has been given to rehabilitation of the affected limb in cases with unilateral impairments following damage to the central (stroke, or TBI) or peripheral nervous systems (amputation, peripheral nerve and/or orthopedic injury). Chronic unilateral amputees provide a remarkable opportunity to understand how skills formerly performed with the now missing dominant hand are reorganized for performance with the non-dominant side. We created an experiment plan and designed an apparatus for a new fMRI project ("intermanual transfer"). This project tested the transfer of the fine motor skills (e.g. writing) between hands, comparing immediate transfer in healthy controls against long-term transfer in dominant hand amputees. We also pilot tested healthy controls.

2. Effects of unilateral upper extremity amputation on brain functional and macroscopic gray matter structure.

A. Activation of the former sensorimotor hand territory top-down with motor imagery and virtual visual feedback. Eleven upper limb amputees participated in an fMRI study designed to investigate the effects of imagery and mirror therapy on the brain of chronic amputees. In this study we showed that moving the intact hand with motor imagery and mirror visual feedback further modulates the former hand representation in the deafferented M1/S1. A manuscript reporting these results was submitted to a top-notch peer-reviewed journal.

B. Characterizing the impact of chronic upper limb amputation on gray matter volume and structure. Long-term structural effects of upper limb amputation were investigated using T1-weighted structural MRI acquired from 26 unilateral, upper extremity amputees. We employed voxel-based Morphometry (VBM) analysis to compare structural images of the hemispheres contralateral and ipsilateral to the amputated hand in a voxel-by-voxel fashion in order to detect differences in local gray matter volume that could then be ascribed to the long-term effects of amputation. Specifically, we expected to find reduced gray matter density in the thalamic regions of the hemisphere contralateral to the amputated hand compared to the ipsilateral hemisphere. We ran the whole brain analysis and began to examine the results. We conducted an ROI analysis to focus on the sensorimotor hand areas (characterized functionally on the basis of control fMRI data), and thalamus (see Figure 2 from the quarterly report).

3. Multivariate statistical approaches to characterization of sensory-motor reorganization following unilateral upper extremity limb amputation.

A. Volitional movements. We collected motor fMRI (and structural) data on 17 upper-extremity amputees: 4 above-elbow right side amputees, 7 below-elbow right side amputees, 5 above-elbow left side amputees, and 1 below-elbow left side amputee. The motor task comprised paced movements of each land, lips, and toes. Below-elbow amputees were instructed to use the forearm muscles that would control the missing hand during the movements, and above-elbow amputees were instructed to imagine moving the missing hand. Preliminary analysis using group independent component analysis (ICA) identified several brain networks involved in motor control, some of which were involved in all voluntary movement and others of which were effector-specific. We showed examples of group-level ICA components in the figures presented in the quarterly report. An advantage of the ICA over conventional general linear modeling approaches is sensitivity to inter-individual and inter-regional differences in the hemodynamic response. This distinction may lead to improved sensitivity in our efforts to characterize amputation-related reorganizational changes.

B. Somatosensory stimulation. We collected somatosensory fMRI data on 14 upper-extremity amputees: 3 below-elbow right side amputees, 5 above-elbow right side amputees, 5 below-elbow left side amputees, and 1 above-elbow left side amputee. In this experiment, subjects experienced light puffs of air delivered to each side of the face and the healthy hand. There were reasons to believe that responses in the somatosensory system would be complex, and would involve both transient and sustained components that are not well-characterized by approaches assuming a canonical hemodynamic response function. This was an area in which we hoped our multivariate ICA approach would provide substantial advantages for characterizing amputation-related reorganizational changes at the individual subject and group levels.

C. Resting state fMRI. Resting state BOLD fMRI has been recognized as having considerable potential for understanding functional connectivity between brain regions, and how these relationships diverge in various patient populations. We employed this technique to investigate how unilateral upper extremity affects functional interactions between widely distributed regions involved in sensorimotor functions. We collected resting state fMRI data on 22 upper-extremity amputees: 6 below-elbow right side amputees, 8 above-elbow right side amputees, 5 below-elbow left side amputees, and 3 above-elbow left side amputees. In this experiment, subjects were asked to relax and fixate on a cross for six minutes. We used this data to answer questions about changes in functional connectivity in the brain after loss of a limb.

We collected data for healthy age-, sex-, and handedness-matched controls for all three fMRI experiments. We also preprocessed the data from the amputee subjects. In the course of

preprocessing, we ran an independent component analysis on each subject's data and visually inspected the results in order to filter out components due to noise. We showed examples of components due to motor activation and due to head movement in the figures in the quarterly report. Both examples came from the same right-side above-elbow amputee.

Project 2: Understanding the consequences of traumatic brain injury on individual brain networks related to executive function (coPIs: van Donkelaar & Mayr)

In summer of 2009, we recruited 2 new chronic TBI patients and ran them through the protocol. We aimed to recruit two matched controls, and run them through the protocol simultaneously, for a total of 7 TBI and 5 control subjects. We initiated a collaboration with colleagues at the VA Puget Sound for purposes of recruiting veterans with TBI. As part of this collaboration we submitted two grant applications.

In the fall of 2009, we recruited and collected data on 4 new chronic TBI patients and 1 control subject. We recruited 1 additional chronic TBI patient and 2 additional controls for testing. In total, we had 10 TBI and 8 control subjects. We presented results from this set of data at the International Brain Injury Association Conference in Washington, D.C. in March 2010. We continued collaboration with colleagues at the VA Puget Sound on grant submissions to the DoD (an Investigator-Initiated Grant), VA (Merit Award) and CDC (Project Grant). **(From D2)**

In the winter of 2010, final TBI subjects required to complete the protocol were tested and 3 additional control subjects were recruited for testing.

A manuscript describing examining the structural-functional relations in TBI using a combination of diffusion-weighting and fMRI imaging along with a motor behavioral task was submitted for publication.

Data have now been collected from 10 TBI subjects and 10 controls. The graduate student collecting this data completed the fMRI analysis and defended her dissertation. Her main finding was that, although participants with TBI performed in a similar manner to controls, they nevertheless recruited a greater extent of their brain to complete the simplest versions of the tasks. By contrast, the controls showed the largest increase in brain activation when going from the simpler to the more difficult version of the tasks. This general finding was in line with several previous fMRI studies of cognition in TBI participants.

Project 3: Developing mice lines capable of reversibly expressing transgenes with an anatomical specificity relevant to neurorehabilitation strategies in humans (PI: Kentros)

Summer of 2009 was a productive time that set the stage for future success. As stated in earlier reports, we shifted our emphasis from the generation of transgenic mice using BAC transgenics, which were not fruitful, towards the more traditional minimal promoter transgenic lines that we (and many others) have had success with. We have since worked on two main goals, transgenic mice which can "silence" neurons (e.g. tetO-AlstR silencer lines we generated in prior quarters), as well as mice capable of expressing the transgenes capable of determining cell-specific connectivity. The former goal is aimed at determining what happens to downstream neurons when presynaptic activity ceases (one of the several aspects of brain trauma), and the latter is aimed at figuring out the connectivity that is affected. Both of these projects turned out well.

In collaboration with the Wehr lab at the University of Oregon, we demonstrated the silencing of sound-evoked neuronal responses in intact auditory cortex of a cross from our Allatostatin silencer mice following superfusion of the pial surface with the silencer transgene's ligand, AL, published in the *Journal of Neurophysiology*. We have been attempting to work out techniques for silencing in awake, behaving animals. We saw evidence of silencing *in vivo*, but results were inconsistent, probably due to difficulties with AL application and/or inconsistencies of transgene expression due to presumed epigenetic silencing. Accordingly, we generated a new injection construct that combined AlstR with GFP, to facilitate *in vitro* work, and to obtain new AlstR founders that express more consistently. As reported in the fall of 2009, although the lab moved forward on other fronts, the silencing work slowed down significantly, and trouble-shooting took great effort. Experiments in our lab and in Michael Wehr's lab (our collaborator) simply stopped working. Post-hoc in situ hybridization analysis revealed an unexpected change in the transgene expression of the payload line: it simply stopped expressing in certain crosses, although we saw tTA expression. This instability of expression is a known issue with transgenesis; we and others have seen it before, but it was a setback. In the winter of 2010, we began to see progress in troubleshooting the AlstR silencer. We set up a slice rig (in the Wehr lab) and an acute electrophysiology rig to record from the silencer animals with a higher throughput than possible with awake, behaving animals. Both of these rigs started to obtain data, and we established crosses for these experiments. We also generated several new AlstR lines, combining AlstR with GFP and AlstR with DS-WGA; one of the former and two of the latter new lines appeared to express the transgenes vigorously. In spring 2010, we resolved or obviated problems with the allatostatin silencer line, by starting to use the new lines that we created in the previous quarters. A handful of the new lines express beautifully, and some of them also express GFP, greatly facilitating *in vitro* work, via our collaborators in the Wehr lab. We saw evidence of ligand-inducing silencing in the slice with one of these lines, and we got the anesthetized prep up and running. Both activities bode well for the future. We also created and injected constructs which expressed other forms of neuronal silencers from the tetO element,

including one of the VAMP-MIST inducible blockers of transmitter release developed by the Svoboda lab, and the ivermectin-sensitive Cl-channel developed by the Lester lab.

The TVAG tracer system has been extremely successful. Since the experiments were relatively quick, we generated enough data to submit a paper demonstrating the utility of this system. The recombinant rabies infects only the transgenic neurons, and then labels only those neurons that are directly presynaptic to them. We learned how to use it, and we determined which lines "leak" by seeing whether virus injection leads to infection via TVA. We crossed the initial seven TVAG/tetO lines to a variety of tTA driver lines and analyzed their expression patterns to add in subsequent tracing experiments in the coming quarters. The TVAG rabies tracer system remained extremely successful. We submitted a paper to *Journal of Neuroscience* detailing the technique, and, as we started to see similar transcriptional silencing of the transgenes, we reinjected the construct to get more founders. We crossed the initial seven TVAG/tetO lines to a variety of tTA driver lines and clearly demonstrated proof of principle, the system stops at a single synapse. The paper we submitted to the *Journal of Neuroscience* detailing the technique was accepted, and we started the crosses to use the technique to detail the connectivity of particular cell types.

We also generated an injection construct for the tetO line that combines the transynaptic tracer WGA (wheat germ agglutinin, labeled with DS-red) with the AlstR receptor, which we are presenting at the Society for Neuroscience in San Diego this year. This will enable us to determine the consequences of the silencing of specific neurons on their postsynaptic partners. This translates into an ability to study the effects of loss of activity on neurons, one of the many consequences of brain trauma, in isolation, i.e. without the confounding effects of inflammation or hypoxia.

Finally, although we shifted most of our efforts towards the above, more tractable aims, we were nevertheless successful in generating a founder from the final BAC transgenic construct, designed to express tTA in neurons of the prefrontal cortex via the DRD4 promoter. We also put ourselves in the queue for the University of Michigan's Transgenic Facility, which has extensive experience with BAC transgenics, to see whether our lack of success to date had to do with our facility's relative inexperience. We also began to increase our capability to expressing tTA in interneuron subtypes. We initiated a collaboration with the Allen Institute to use a parvalbumin-tTA expressing mouse, and we designed an injection construct that should drive tTA expression from the calbindin promoter.

Aim 2: Telemedicine and Neuroinformatics

Project 1 – High Performance Signal Analysis Toolkit for Dense Array EEG

In the summer of 2009, our work continued in all areas described in previous reports. Bob Frank optimized DCA's blink detection algorithm for identifying intervals of blink contaminated data. DCA was made compatible with EGI's eye tracker software, which independently identifies intervals of eye-blink and eye-movement contamination. Based on the results of a comprehensive statistical test of DCA's performance on 32- 128- and 256-channel EEG data sets, we planned to incorporate DCA into the future Net Station release and undergo continued refinement.

Side by side with DCA algorithm development in Matlab, Chris Hoge built C++ versons using the VSIPL++ package. He also worked with the CIS student, Nicholas Boydston, on CUDA-based ICA algorithms.

Progress was made on NEMO to port the autolabeling code, which generates spatio-temporal metrics for ERP component identification and labeling, to a Matlab object-oriented framework to facilitate its use by NEMO consortium members. Work accelerated on incorporating clustering algorithms to utilize the extracted metrics for pattern recognition/clustering. Bob Frank annotated the extracted spatio-temporal feature metrics in RDF (Resource Description Framework) format to facilitate to code's ability to link to the corresponding entities in the NEMO ontology. We planned to test at least 2 new TBI patients and several controls on the behavioral manuscript as well as submit a new manuscript examining structural-functional relations in TBI using a combination of diffusion-weighting and fMR imaging along with a motor behavioral task.

During the fall of 2009, the first version of the Matlab object-oriented framework, developed by Bob Frank, was realized. Further activities involved building support in Matlab and the NEMO database for automating analysis pipelines. Most of the results were internal in the restructuring of Matlab code.

John Sydes achieved an initial deployment of a NEMO database, which can store raw and processed EEG waveforms, as well as statistical measures from application of component analysis and autolabeling. Mr. Sydes also made good progress in the development of a NEMO portal.

In the winter of 2010, we submitted, published, and presented several papers, and achieved an important demonstration milestone in computational head modeling. The work involved a full team effort and resulted in a paper submission to the SC10 conference.

The Matlab object-oriented framework, being developed by Bob Frank, was introduced at the NEMO Consortium meeting in Atlanta, GA, in February 2010. The framework consists of components for the decomposition of event related potential (ERP) data, and subsequent quantization of their spatiotemporal properties. As we noted in the quarterly report, this will

significantly facilitate NEMO consortium members' signal analysis toolkit access and provide a robust foundation for the future Matlab code development of dense-array EEG data analysis tools. Further activities focused on porting earlier Matlab-based ERP and EEG analysis tools into Matlab sub-classes of the signal analysis toolkit's object-oriented framework. This will provide for a common code base to maximize code reuse and provide a more consistent user interface for the NEMO consortium members. Most of the results involved internal restructuring of Matlab code.

We added a new statistical analysis method, *Topographic Analysis of Variance (TANOVA)*, to the signal analysis toolkit. TANOVA can detect statistically significant variations in ERP topographies between experiment conditions, and support understanding of how changes in experimental stimuli between conditions affect cortical processing.

Chris Hoge completed development of tools to manage and visualize workflows created in the NIC workflow system. In the quarterly report, we presented a figure of the integration of the NIC workflow system in the multi-tiered NIC application architecture. The objective was to provide a high-level workflow specification and management support to leverage system capabilities for execution. An initial workflow to capture the steps for computing brain conductivity was developed and was captured in a graphic in the same quarterly report.

The tools Hoge created for visualization are useful both in the workflow design process as well as for monitoring of workflow progress.

In the spring of 2010, we focused on creating end-to-end capabilities for computation head modeling workflow.

Bob Frank continued development of the Matlab-based object-oriented framework. Work focused on connecting extracted signal metrics to the NEMO ontology through the use of RDF (Resource Description Format) formatted output. RDF incorporates URI references (Uniform Resource Identifiers) that link the metrics to definitions and relationships encoded within the ontology. With further refinement, this will enable users to query the ontology via the SPARQL RDF query language, to find which ERP patterns of interest are captured by the experimental data as described by its extracted metrics.

Further activities provide for a common code base to maximize code reuse and provide a more consistent user interface for the NEMO consortium members. Most of the results are internal restructuring of Matlab code.

Bob Frank also completed the integration of the Smart-Eye eye tracker system into the DCA (Directed Components Analysis) framework for the extraction of ocular artifacts from continuous EEG recordings. Temporal intervals of eye movements and eye blinks, identified by

the Smart-Eye system, were marked and passed to DCA for subsequent removal. Current work focused on writing new code to allow DCA to work with a wider array of EEG file formats.

Chris Hoge continued development of his workflow system and worked with lab staff to implement workflows for TATRC projects. He extended the workflow system with a web-services front end to allow automated applications to query the status and control of workflows. Web-services will be provided as a hybrid Representational State Transfer (REST) and Remote Procedure Call (RPC) system. Security and access to the system will use a multi tiered approach with secure HTTP to encrypt requests, keys provided for institutional or application access, and a "shared secret" mechanism for signing requests. By using this web-services framework it will be possible for new applications (such as research or medical equipment) to integrate with the workflow system without the need of an individual using a web browser.

Work continued on implementing workflows within the system. After completion of the pilot task of selecting a subject with associated data, and processing that data in BrainK, we began a workflow for using EEG data alongside MRI data to create a head conductivity map. The goal of a workflow will be to allow a non-expert trained in using the workflow system to run a complete conductivity study on a large set (~100 subjects) of data.

Project 2 – MRI and CT registration for accurate source analysis

In the summer of 2009, Dr. Turovets directed work on the normative conductivity data collection in CDS. The new research assistant, Brian Esler, helped Dr. Turovets set up and run experiments on conductivity scanning in human trials and phantom validation experiments. The regular conductivity scans were performed routinely, approximately twice a week, with the pool of subjects who underwent the normative MRI scans (see below). Several improvements and upgrades to the scanning software and protocols were made as results of the human trials analysis. In particular, the new strategy to deal with electrolyte bridges (combined use of the hydrogel and saline), and to handle and process the raw impressed EEG data were developed.

Data from the full RMI sequence (previously elaborated) on 96 normals (no history of TBI) was collected. All 100 subjects were done by October, 2009. Resting EEG and EIT was collected on 7 of the 96 participants for whom we have MRIs (3 of whom also have whole-head CTs).

In the area of MRI imaging analysis, more capabilities were added to Dr. Li's BrainK tool. In particular, CT segmentation was added to the future set, and work on aligning CG and MRI images was been completed. Furthermore, GPS sensor registration with the head model was implemented in the last quarter.

Using BrainK, Dr. Li performed a highly accurate MRI segmentation on the Atlas Man in an attempt to recognize extremely thin structures, such as the alveus of the hippocampus, which are difficult to segment with automatic algorithms. Some manual intervention was required. One of the goals of this effort was to build a segmentation template to further improve BrainK's automatic segmentation performance.

The MRI imaging scanning was completed in fall 2009. We now have a large database ready for full head model construction and conductivity processing

Dr. Kai added a major feature in BrainK in the area of Talairach transformation. Given the anterior commisure point, the posterior commisure point, and a point in the middle sagittal plane, BrainK is now able to automatically transform the original MRI data and the brain segmentation results into Talairach space. Dr. Li additionally developed techniques to register the GPS sensors with the transformed model, as well as generate dipoles (7 mm triples) in Talairach coordinates. BrainK will support the Talairach transformation of the cortical surface as well as the dipoles on the surface.

During the winter 2010 quarter, Dr. Kai Li completed the Talairach transformation for a set of data types including raw MRI, segmentation, cortex volume and mesh, dipoles, cranium normals, and EEG sensor positions. Topology correctness was maintained for the cortex. Consistency between different data was also enforced. He worked on the mapping of dipoles to an atlas cortex flatmap and using cortical surface inflation for better visualization of source localization results.

With the achievements of the NIC's electromagnetics head modeling, the NIC enhanced its activities in constrained source localization methods. Dr. Hammond focused on developing the algorithmic framework for using graph-based regularization for EEG source localization. This methodology is situated in the context of the distributed dipole framework, where the desired electrical activity in the brain is described with a fixed dense set of source dipoles. The graph regularization is based on treating these dipoles as vertices of a "connectome" graph, with weighted edges measuring the connectivity of cortical regions. A graph smoothness prior, which penalizes patterns of electrical activity with changes over connected edges, can be used to regularize the inverse problem of estimating cortical sources.

Dr. Hammond showed that using a quadratic graph smoothing prior with a standard least-squares data fidelity term led to a closed form linear solution for source localization. He began to develop a framework for temporal regularity to allow introducing prior knowledge of the frequency content expected at different brain locations.

In spring 2010, Dr. Kai worked on the eyeball segmentation problem. BrainK can automatically segment the eyeballs in MRI by determining the center location and the radius of the spherical

balls. This procedure is added as an intermediate module in BrainK and the eyeball segmentation result is integrated within the final head tissue result, which includes the following tissue types: WM (white matter), GM (gray matter), CSF (cerebral spinal fluid), bone, flesh, air inside the head, aire outside head (background), and eyeballs. Given the success with the eyeball segmentation, we look to further segment the eye socket and optical nerve.

Dr. David Hammond's recent work at the NIC has focused on continuing the development for graph-based techniques for EEG source localization. The overall goal of this project was to use knowledge of brain connectivity, as measurable by non-invasive fiber tract tracing from MRI data, to construct a prior model for cortical electrical activity. We planned to use this prior model in the context of the distributed dipole framework provided by forward modeling of head electrical conduction to identify cortical sources.

The foundation of the graph-based prior is the creation of connectivity vertices corresponding to cortical regions associated with electrical dipoles. Before the introduction of actual tractography data, Hammond pursued assembling the graph-based methodology using a cortical adjacency graph, where cortical regions are connected if they are contiguous on the cortical surface. In collaboration with Dr. Gwen Frishkoff at Georgia State University, he began to apply the graph-based methods for localization of motor potentials in a voluntary button-pressing task. Both the dipole-scale cortical adjacency graph and the lead field matrix for an individual subject in a motor potential study were successfully computed. Preliminary source analysis on the ERP data was also begun.

Project 3 – Head tissue conductivity analysis

In the summer of 2009, we continued to develop new algorithms to solve the 3D electromagnetic problems associated with EEG and EIT, and process experimental data in phantom experiments and human trials. Two papers on these topics were submitted to International Conference on Electrical Bioimpedance held April 4-8, 2010 in Gainesville, Florida. An efficient numerical method was developed for solving the isotropic inhomogeneous 3D Poisson equation in cylindrical coordinates as applied to analysis of EIT phantom experimental systems. The approach utilizes the cylinder symmetry and is based on a second-order accurate finite-difference scheme and a preconditions BiCG iterative method. Extensive validation f the method and comparison with experimental results were conducted. The performance and accuracy of the proposed numerical method is compared with the similar finite difference method in the Cartesian coordinates and the finite element method on the adaptive grid. We investigated how to further improve the method using compact finite difference schemes with

spectral-like resolution. We planned also to parallelize the BiCG algorithm with OpenMP/MPI on a multicore cluster and assess its parallel performance against the vector-additive mthods.

A Ph.D. student, Stas Kounitsky, worked with Dr. Sottile and Dr. Malony to port the new vector-additive implicit method for the anisotropic head model to CUDA for execution on a NVIDIA GPU. Preliminary results on performance tests showed the speedup factors of 20-40 compared to to the sequential C++ version of the code.

Chris Hoge established a workflow that included all the input data and transformation necessary to create a head model, conduct the conductivity modeling process, and build a lead field matrix result. This workflow was eventually developed into a working system to provide results that could be reproduced and analyzed. This included overseeing the development of a BrainK interface by the Oxyent Medical group.

In the fall of 2009, Drs. Vasily Volkov and Sergei Turovets, together with Dr. Volkov's Ph.D. student, Aleksei Zherdetsky, developed a fast solver for electrical impedance tomography (EIT) and applied this tool to human head analysis. Dr. Turovets had also used the new EIT analysis algorithms in processing experimental data from phantom experiments and human trials. Two papers on these topics were accepted to the International Conference on Electrical Bioimpedance, held April 4-8, 2010, in Gainesville, Florida.

The results of two types of the EIT experiments with a cylinder tank filled with saline and agar gel insertions were processed: piecewise constant domain conductivity estimations (bEIT) and difference imaging. The forward and inverse modeling were performed with our in-house FDM BiCG solvers in the cylindrical coordinates with the FFT preconditioner and also within an open source FEM software suite, EIDORS. Our preliminary results demonstrated efficiency of the BiCG solver for inverse problems in phantoms with the cylinder symmetry and great promise of the conductivity scanning technology for improving source localization in an analysis of brain electrical activity.

Stas Kounitsky successfully completed the port of the new vector-additive implicit (VAI) method for the anisotropic head modeling to CUDA for execution on the NVIDIA GPU. The new VAI method, developed by Dr. Volkov and Dr. Turovets, showed significant speedup, compared to the sequential C++ version of the code. Mr. Kounitsky additionally implemented a shared-memory multi-threaded version of the algorithm using OpenMP.

Chris Hoge continued developing a generic scientific workflow system for the conductivity modeling work. A workflow was modeled as a graph of task nodes connected by input/output edges**.** Tasks assigned to nodes can be either computational processes that are scheduled and run from a thread pool, or user querying a user for input. Some defining characteristics of the workflow system is database backed storage to be used for scientific analysis and replication of

results. Scientific studies in the system are supported by a workflow cloning idea in which a complete copy of a workflow can be created at any stage of its completion, allowing for exploration of parameter space at any stage of an experiment.

Mr. Hoge also completed work with Oxyent Medical group on the BrainK interface. Work moved forward to integrate the lessons learned from that experience without online normative database.

In winter of 2010, we made advances in several activities in the area of electromagnetics head modeling. Because the forward solver is the core of the bEIT conductivity inverse and lead field matrix (LFM) calculations, it was important to 1) validate the accuracy of forward solver as best as possible, and 2) implement the forward solver to run as fast as possible. The NIC developed two forward solver methods: the Alternating Difference Implicit (ADI) for isotropic head models, and the Vector Additive Implicit (VAI) for anisotropic head models. The ADI method was previously validated and its implementation in OpenMP and CUDA previously reported. Work focused on the VAI solver.

Drs. Vasily Volkov and Sergei Turovets made the final validation of the VAI anisotropic numerical algorithm in the isotropic setting against spherical model analytics both in EIT and dipole modes. In addition, validation was made in the anisotropic setting against anisotropic dipole analytics. Stas Kounitsky enhanced the VAI ported to OpenMP and CUDA for parallel execution. Dr. Adnan Salman applied both ADI and VAI in processing the comprehensive experimental set of the Atlas Man bEIT conductivity scans (64 pairs for ADI, 4 pairs for VAI). In addition, a LFM for Atlas Man was generated by Dr. Salman for ADI and VAI. This combined work resulted in the NIC creating its first real head model for use in source localization. We submitted a paper describing this achievement to the International Conference for High Performance Computing, Networking, Storage, and Analysis (SC10).

Dr. Turovets, together with Aleksei Zherdetsky, upgraded the fast BiCG solver for electrical impedance tomography (EIT) to compute the induced magnetic field *Bz*, which makes this solver applicable for the EIT extended modality, Magnetic Resonance EIT (MREIT). In inverse problem with phantoms, the data from as many as 120 experimental injection pairs were processed using this fast forward solver and the standard optimization function, *fmincon*, from the Matlab optimization toolbox, based on the multi-start Gauss-Newton method. The extracted estimates were in agreement with *a priori* known (directly and independently measured) conductivity values of saline solutions and agar insertions in the phantom. Similar results were also obtained with the open domain FEM software suit, *EIDORS*, together with another research assistant, Brian Esler. Thus, it was proven that in the low-dimensional space of conductivity unknowns inverse optimizers based on the deterministic approach (like the Gauss-Newton methods) can be employed with confidence. Two papers on these topics were

presented by Dr. Turovets at the International Conference on Electrical Bioimpedance on April 4, 2010. Another paper was accepted for the 16th Annual Meeting of the Organization for Human Brain Mapping (OHBM 2010), June 6-10, 2010, and two conference papers were submitted for the 29th international Congress of Clinical Neurophysiology (ICCN2010), October 28 – November 1, 2010.

Dr. Adnan Salman led the computational head modeling work, for purposes of conductivity analysis. He implemented the computation of the subject-specific lead field matrix (LFM) with oriented dipoles. This approach is preferred because the oriented dipoles best capture their physical placement relative to cortex normals. He was evaluating the importance of the specific LFM and the anatomically constraint dipole orientations positions. Salman also included the use of reciprocity principle in the computation of the electromagnetics forward problem. This will be useful for performance enhancement of LFM generation and will improve the potential use of the equivalent dipole model in source localization

With respect to conductivity evaluation, Salman formulated a plan to conduct a sensitivity study to investigate the effect of skull sutures and fontanelles on the forward and inverse problems. The goal is to rank the measuring sensors sensitivities to the brain conductivity to improve the accuracy of the forward solution and conductivity modeling.

Dr. Sergei Turovets developed an FDM formulation for a forward solver in the EIT extended modality, Magnetic Resonance EIT (MREIT), and completed the first initial runs in Matlab for cylindrical phantoms (in collaboration with Dr. Volkov). In general, the MREIT forward solver was able to deal with arbitrary shapes and compute the induced magnetic field for a given current injection pattern. The work was also conducted with the open domain FEM software suit, EIDORS, together with a research assistant, Brian Esler, on inverse conductivity estimates for experimental phantom data and difference EIT imaging. The results were presented in conference papers in EIT 2010 in Gainsville, FL, and are being prepared for an extended full length journal paper. Three sets of human bEIT conductivity scanning data (out of 17 scanned to date) were processed and a paper presented at the 16th Annual Meeting of the Organization for Human Brain Mapping, OHBM 2010, June 6-10, Barcelona, Spain.

MAJOR REPORTABLE OUTCOMES

Papers published

A. Zherdetsky, V. Volkov, S. Turovets, and A. Maloney, “A fast BiCG solver for the Isotropic Poisson Equation in the Forward EIT Problem,” *International Conference on Electrical Bioimpedance*, April 4-8, Gainesville, FL, 2010.

B. Esler, T. Lyons, and S. Turovets, "Instrumentation for Low Frequency EIT Studies of the Human Head and its Validation in the Phantom Experiments," *International Conference on Electrical Bioimpedance*, April 4-8-, Gainesville, FL, 2010.

D. Hammond, P. Vandergheynst, R. Gribonval, "Wavelets on Graphs via Spectral Graph Theory," *Applied Computational and Harmonic Analysis* February, 2010.

P. Luu, R. Frank, S. Kerick, and D. Tucker, "Direct Components Analysis: an Analytic Method for the Removal of Biophysical Artifacts from EEG Data," *Human Computer Interface (HCI)*, July, 2009.

Weible AP, Rowland DC, Pang R, Kentros C. "Neural correlates of novel object and novel location recognition behavior in the mouse anterior cingulate cortex," J *Neurophysiol.* 2009 Oct; 102(4):2055-68. Epub 2009 Jul 8

Dissertation

"A software framework for simulation-based scientific investigations," AdnanSalman, Ph.D. thesis, Department of Computer and Information Science. University of Oregon, December, 2009.

Proposals Awarded

"MRI-R^2: Acquisition of an Applied Computational Instrument for Scientific Synthesis (ACISS)," A. Maloney (PI), J. Conery (co-PI), D. Tucker (co-PI), M. Guenza (co-PI_, S. Lockery (co-PI), proposal to the NSF Major Research Instrumentation (MRI-R^2) program, $1,998,560, August, 2009.

Presentations/Conference Papers accepted

A. Zherdetsky, V. Volkov, S. Turovets, and A. Maloney, "A fast BiCG solver for the Isotropic Poisson Equation in the Forward EIT Problem," *International Conference on Electrical Bioimpedance*, April 4-8, Gainesville, FL, 2010.

B. Esler, T. Lyons, and S. Turovets, "Instrumentation for Low Frequency EIT Studies of the Human Head and its Validation in the Phantom Experiments," *International Conference on Electrical Bioimpedance*, April 4-8-, Gainesville, FL, 2010.

D. Hammond, “Wavelets on Graphs via Sprectral Graph Theory,” presented at the Pacific Northwest sectional meeting of the Mathematical Association of America, Seattle, April 10, 2010.

D. Hammond, “Image Denoising with Nonlocal Spectral Graph Wavelets,” presented at the *SIAM Imaging Sciences Conference*, Chicago, April 13, 2010.

Frey, S.H., Bogdanov, S., Watrous, S., & Smith, J. *“Seeing an amputated hand touched increases activity in multisensory areas of the human posterior parietal cortex.”* Presented at the Annual Meeting of the Society for Neuroscience. Chicago (November, 2009).

M. J. Sottile, G. Hulette, A.Maloney, “Workflow Representation and Runtime Based on Lazy Functional Streams.” *Workshop on Workflows in Support of Large-Scale Science (WORKS)*, held in conjunction with *Supercomputing 2009 (SC09)*, Portland, OR, 2009.

S. Turovets, A. Salman, K. Li, A. Malony and D. Tucker. “Towards Subject Specific Head Models for Improved High-Resolution EEG.” *16-th Annual Meeting of the Organization for Human Brain Mapping (OHBM 2010)*, Barcelona, Spain, June 6-10, 2010.

V. Volkov, A. Zherdetsky, S. Turovets, and A. Malony, “A Fast BiCG Solver for the Istoropic Poisson Equation in the Forward EIT Problem,” *International Conference on Electrical Bioimpedance*, April 4-8, Gainesville, FL, 2010.

Conclusion

Projects are close to closure on this award with some work remaining on Aim 1, Project 2. A final report will be forthcoming after the closeout date of March 2011.